

**APPLICATION FOR  
UNITED STATES LETTERS PATENT  
IN THE NAME OF**

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**ASSIGNED TO**

**ADVANCED MEDICAL OPTICS, INC.**

**FOR**

**CETYLPYRIDINIUM CHLORIDE AS AN ANTIMICROBIAL AGENT  
IN OPHTHALMIC COMPOSITIONS**

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## **CETYLPIRIDINIUM CHLORIDE AS AN ANTIMICROBIAL AGENT IN OPHTHALMIC COMPOSITIONS**

### **BACKGROUND OF THE INVENTION**

#### **Area of the Art**

The present invention relates to compositions and methods for eye and contact lens care. More particularly, the invention relates to ophthalmic compositions which contain cetylpyridinium chloride as a decontaminating agent for preservation of the solution and/or disinfecting contact lenses.

#### **Description of the Prior Art**

Contact lens wear induces adverse changes in ocular tissues and the tear film. These changes include cornea lactic acidosis and subsequent cornea swelling as a consequence of hypoxia induced by low oxygen gas transmission, changes in corneal epithelial tissue thickness, changes in corneal epithelial and endothelial cell morphology, epithelial surface cell exfoliation, hyperemia (red eye), adverse changes in corneal and conjunctival cell membrane integrity and destabilization of the tear film. Changes in cell membrane integrity can be measured clinically via measurements of lactate dehydrogenase enzyme release, fluorescein barrier permeability or other methods. Corneal epithelial cell membrane integrity is believed to be critical to maintain a tissue barrier function to prevent ocular infection.

Adverse changes in ocular tissues during contact lens wear also may arise due to exposure of ocular tissues to preservatives, disinfecting agents, cleaning agents and other components in the contact lens care solutions. This can occur through tissue contact with solutions which may directly contact ocular tissues during application or tissue contact with

solutions which may absorb to the contact lens during treatment of the contact lens by the solution, and subsequently desorb from the contact lens during wear into the eye.

Contact lens solutions have become complex formulations of multiple components which provide several functions. Attempts have been made to ameliorate the adverse effects of contact lenses and contact lens care solutions on ocular tissues, with mixed results. The best examples of success in changing contact lens care solutions to ameliorate their adverse effects on ocular tissues is represented by the creation of polymeric contact lens disinfecting agents, antimicrobial systems which do not bind to contact lens surfaces and the inclusion of water-soluble polymers and electrolytes such as potassium chloride, magnesium and calcium chloride into contact lens multi-purpose and rewetting solutions. However, despite these favorable changes in the compositions of contact lens care solutions, none provide perfect in-eye performance without some measure of adverse effect on ocular tissues. Some degree of compromise to the tear film, tissue or cellular membrane integrity, such as corneal epithelial cell membrane integrity, remains with all current contact lens care solutions.

To date users have shown some preference for the polymeric biguanide quaternary ammonium based systems, which combine three steps of cleaning, disinfecting and rinsing in one. However, polymeric quaternary ammonium systems are usually weak in anti-fungal activities. Moreover, because of the positively charged nature of the polymeric biguanide and quaternary ammonium antimicrobial agents, they tend to be heavily adsorbed or bound to the contact lens materials (which are usually negatively charged), causing eye irritation. Therefore, there exists a need to improve contact lens care products to provide for simpler use with higher antimicrobial potency and less cornea irritation.

It is desirable to formulate a system having stronger anti-microbial properties than known systems, without increasing the adverse effects of contact lenses and contact lens care solutions on ocular tissues.

Previously it was thought that cetylpyridinium chloride (CPC), while useful as an anti-microbial agent for personal care product preservation, medical device disinfection and environmental decontamination, was unsuitable for use in soft contact lens cleaning solutions due to irritation to the eye caused by buildup in the contact lenses. Such irritation is believed to be caused by stimulation of the anterior ocular segment tissue, which may cause allergic reactions, inflammation, corneal erosion and the like. See, e.g., U.S. Patent No. 4,908,147, to Tsao et al., which teaches that conventional quaternary germicides, such as benzalkonium chlorides, CPC and dodecyl triethanolamine hydrochloride tend to accumulate in hydrophilic soft contact lens materials. Similarly, Doi et al., in U.S. Patent No. 5,994,405 note that bacteriocidal agents such as CPC are known to be readily adsorbed, particularly onto soft contact lenses. Once adsorbed, such bacteriocidal agents are hardly released, but accumulate on the lenses.

US 3,954,644, to Krezanoski et al., teaches that cetylpyridinium chloride is a germicidal agent that is compatible with flexible silicone lenses, and is effective in concentrations ranging from about 0.001 to 0.03 percent of the overall solution. As is well known in the art, flexible silicone lenses are typically formed from silicone rubber, and are oxygen permeable, so they may be worn by the user for weeks on end. This may be contrasted with conventional soft contact lenses, which are hydrophilic lenses typically formed from a hydro-carbon polymer and which form hydrogels in equilibrium with water. Such soft contact lenses are typically water permeable, but not oxygen permeable, so it is typically recommended that the user remove their

soft lenses at night. Flexible silicone lenses are also distinguished from silicone-hydrogel soft contact lenses, which also form hydrogels in equilibrium with water.

In the past, others have tried to incorporate CPC in ophthalmic solutions. For example Shinohara et al., in U.S. Patent No. 5,998,488, teach the use of CPC as an antimicrobial preservative. However, Shinohara et al. also teach that a compound such as cyclodextrin must be included in the ophthalmic solution containing CPC at a concentration greater than 0.3% to inhibit the CPC from adsorbing to contact lenses. This is undesirable both from a manufacturing standpoint and from a complexity standpoint.

When used in association with soft contact lenses, high CPC concentration results in high CPC lens uptake, consequently causing high cornea irritation. While contact-lens-adsorption inhibitors may be used, the addition of contact-lens-adsorption inhibitors, such as cyclodextrin, also compromises CPC disinfecting efficacy. To compensate for the reduction of disinfecting efficacy due to the presence of the uptake inhibitors, the concentration of CPC concentration must be raised. This, in turn, results in an increase in CPC lens-uptake and cornea irritation.

In view of known limitations with contact lens care compositions, it would be advantageous to have contact lens care compositions, and methods of using the same, which are simpler to use, have higher antimicrobial potency, and show less corneal irritation.

### Brief Description of the Drawings

FIGURE 1 illustrates an equilibrium data graph plotted showing function of CPC concentration at adsorption.

### DETAILED DESCRIPTION

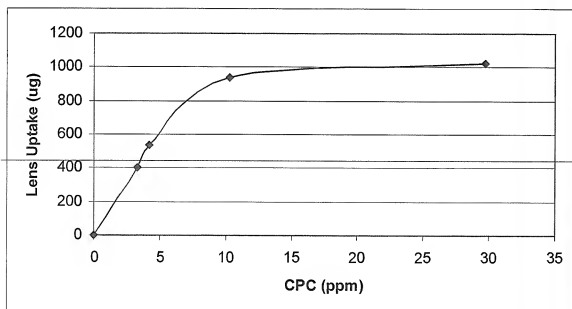
New compositions for treating contact lenses have been discovered. Specifically, it has unexpectedly been discovered that, while a contact lens can become fully saturated with CPC when exposed to solutions containing more than 10 ppm CPC, the amount of CPC uptake from solutions having a CPC concentration that is below 10 ppm by contact lenses is significantly reduced without losing antimicrobial efficacy. As discussed above, prior to the present invention it was commonly believed that CPC at or below 10 ppm was not efficacious as a disinfecting agent. The weak antimicrobial efficacy previously seen was likely due to the interaction between CPC and other ingredients such as surfactants which are commonly added to a product if wetting, solubilizing and cleaning functions are required. This is supported by the data shown in Table 1, which shows that antimicrobial activity reduced to an ineffectual level when 238 ppm tocopherol polyethylene glycol succinate ("TPGS"), a non-ionic surfactant, co-exists with 9.5 ppm CPC, although the solution is still efficacious at 76 ppm TPGS.

It has been discovered that cetylpyridinium chloride (CPC) at low concentrations, in combination with a non-ionic surfactant, can be efficacious as a contact lens disinfection agent. In one embodiment of the present invention, the non-ionic surfactant is a poly(oxypropylene)-poly(oxyethylene) block copolymer. Such efficacy may be seen in concentrations ranging from as low as 0.1 ppm or 0.3 ppm to about 8 ppm, 9 ppm or 10 ppm.

Figure 1 shows the amount of CPC uptake by Purevision® lenses (Bausch & Lomb Incorporated, Rochester New York) as a function of CPC concentration at adsorption equilibrium. The initial solutions are the same as those in Table 5 (below), with the exception of the CPC concentration, which ranges from 5 – 40 ppm in the solutions tested to obtain the data shown in Figure 1. 100 - 200 ml of each of the solutions per lens were used for soaking lenses and, the CPC concentration in each solution was monitored for a period of 12 days. The

equilibria between the concentration of CPC in solution and the amount of CPC adsorbed onto each lens were reached after 6 days of soaking. The equilibrium data were then plotted in Figure 1.

FIGURE 1



The present compositions include, in an aqueous liquid medium, a non-ionic surfactant and cetylpyridinium chloride. In one embodiment of the present invention, the non-ionic surfactant is a poly(oxypropylene)-poly(oxyethylene) block copolymer. Such solutions may also include one or more of the following: additional antimicrobial components, preferably reduced in concentration from the concentration that is typically used with only one antimicrobial component; a buffer component in an amount effective to maintain the pH of the solution within a physiologically acceptable range; an effective amount of a viscosity inducing component; a surfactant in an amount effective to clean a contact lens contacted with the solution; and a tonicity component in an amount effective to provide the desired tonicity to the solution. The solutions may also include taurine. The benefits of including taurine are disclosed in U.S. Patent

Application Ser. No. 10/328,641, to S. Huth, entitled "Contact Lens Care Compositions, Methods of Use, and Preparation which Protect Ocular Tissue," which is incorporated herein by reference. The solutions of the present invention provide the desired antimicrobial activity and performance effectiveness and, importantly, substantial, preferably enhanced, lens wearer/user comfort and acceptability benefits.

There are several obstacles which prevent the use of cetylpyridinium chloride in a contact lens cleaning disinfecting application. First, contact lens cleaning and disinfecting solutions typically contain significant amounts of surfactants in order to clean the contact lens surface which is contaminated mainly by tear protein and lipids. Of the three types of surfactants, non-ionic surfactants are commonly used for contact lens cleaning. However, non-ionic surfactants are also commonly used to neutralize quaternary-based antimicrobial agents in microbiology test labs. Thus, the concentration must be carefully controlled.

Anionic surfactants such as soap are generally not compatible with quaternary amine based antimicrobials that are positively charged. In other words, it is common wisdom that the application of anionic surfactants would defy the microbial activity of non-polymeric based polyquaternary ammonium compounds. Electrostatic interaction between ion of the surfactant and cation of the quaternary ammonium would neutralize the net charge, eliminate the antimicrobial activity and form a precipitate due to the loss of hydrophilicity by charge neutralization.

Cationic surfactants are compatible with alkyl amines, but they themselves are antimicrobial agents, and therefore cannot be added in large amounts without irritating the eye.

The inventors have unexpectedly discovered that CPC is highly active in specific concentration ranges and can be used in contact lens disinfecting. That is, CPC can be used for



contact lens disinfection without significantly building up in a contact lens, provided that it is used with a certain type of surfactant which functions as a cleaning and/or solubilizing agent, and the two are used according to a special mixing ratio. The inventors have further discovered that a certain type of non-ionic surfactant, used in a certain mixing ratio, can reduce CPC lens uptake while maintaining anti-microbial effectiveness for disinfection.

The present compositions, which may be multi-purpose solutions, have a multitude of applications, for example, as disinfecting, cleaning, soaking, wetting, rewetting, rinsing, storing, in-the-eye cleaning, and conditioning compositions, for contact lens care, while providing substantial lens wearer/user comfort and acceptability. The present compositions also increase user compliance, that is promote regular and consistent contact lens care, and, ultimately, lead to or facilitate better ocular health. Any contact lenses, for example, conventional hard contact lenses, rigid gas permeable contact lenses and soft, hydrophilic or hydrogel, contact lenses, including silicone hydrogel contact lenses, can be treated in accordance with the present invention.

Previously, it was believed that, if CPC was to be used in a contact lens-care solution, it must be present at a concentration that is much higher than the present invention in order to demonstrate its beneficial properties. At such concentrations, CPC may undesirably adsorb or absorb to the contact lens during treatment of the contact lens by the solution, and subsequently desorb from the contact lens during wear into the eye. Thus, CPC was undesirable for use in contact lens-care solutions. The inventors have unexpectedly discovered that CPC, in the presence of a selected non-ionic surfactant, can be efficacious as a contact lens disinfection agent at low concentration (<10 ppm).

Examples of some non-ionic surfactants for use in the present invention are disclosed in, for example, Kirk-Othmer, Encyclopedia of Chemical Technology, 3rd Edition, Vol. 22 (John Wiley & Sons, 1983), Sislet & Wood, Encyclopedia of Surface Active Agents (Chemical Publishing Co., Inc. 1964), McCutcheon's Emulsifiers & Detergents, North American and International Edition (McCutcheon Division, The MC Publishing Co., 1991), Ash, The Condensed Encyclopedia of Surfactants (Chemical Publishing Co., Inc., 1989), Ash, What Every Chemical Technologist Wants to Know About . . . Emulsifiers and Wetting Agents, Vol. 1 (Chemical Publishing Co., Inc., 1988), Tadros, Surfactants (Academic Press, 1984), Napper, Polymeric Stabilization of Colloidal Dispersion (Academic Press, 1983) and Rosen, Surfactants & Interfacial Phenomena, 2nd Edition (John Wiley & Sons, 1989), all of which are incorporated herein by reference. By way of example, but not of limitation, such surfactants include Tetronic® 1307, Tetronic® 904, Tetronic® 1304, Tetronic® 1107 (BASF Corporation, Mount Olive, New Jersey) and Pluronic® F87 (BASF Corporation, Mount Olive, New Jersey). By way of further example, and not of limitation, such non-ionic surfactants may include block copolymers, tridecyl alcohol ethoxylates, stearyl alcohol ethoxylates, polyethylene glycol esters, octylphenol ethoxylates, nonylphenol ethoxylates, national formulary block copolymers, lauryl alcohol ethoxylates, glycerol esters, ethylene/propylene oxide block copolymers, ethoxylated sorbitan fatty acid esters, decyl alcohol ethoxylates, amine oxides, amine based block copolymers, alcohol ethoxylates, and alcohol alkoxyates.

The additional antimicrobial component may be any suitable, preferably ophthalmically acceptable, material effective to disinfect a contact lens contacted with the present solutions or alternatively adequately preserve a solution such as a contact lens rewetting solution. Preferably, the additional antimicrobial component is selected from biguanides, biguanide polymers, salts

thereof and mixtures thereof, and is present in an amount in the range of about 0.1 ppm to about 3 ppm or less than 5 ppm (w/v). By way of example, and not of limitation, the additional antimicrobial component may be a monomeric quaternary ammonium or biguanide compound such as chlorhexidine digluconate, chlorhexidine diacetate, benzethonium chloride and myristamidopropyltrimethylamine. The additional antimicrobial component may also be a polymeric quaternary ammonium compound such as Polyquad.RTM. (polyquaternium-1) or poly[oxyethylene (dimethyliminio) ethylene-(dimethyliminio) ethylene dichloride] (sold under the trademark *WSCP* by Buckman Laboratories, Inc.). The preferred relatively reduced concentration of the additional antimicrobial component has been found to be very effective, in the present compositions, in disinfecting contact lenses contacted with the compositions, while at the same time promoting lens wearer/user comfort and acceptability.

Any suitable, preferably ophthalmically acceptable viscosity inducing or thickening agent may be included in the present compositions. The viscosity inducing component preferably is selected from cellulosic derivatives and mixtures thereof and is present in an amount in the range of about 0.05% or about 1.5% to about 3% or about 5.0% (w/v). Without wishing to limit the invention to any particular theory of operation, it is believed that the presence of a viscosity inducing component at least assists in providing the lens wearer/user comfort and acceptability benefits of the present invention, which promote regular and consistent contact lens care and ultimately lead to or facilitate better ocular health. The present combinations of components, for example, including such viscosity inducing components, are effective in providing the degree of lens wearer/user comfort and acceptability benefits described herein.

Although any suitable, necessarily ophthalmically acceptable, tonicity component may be employed, an extremely useful tonicity component is a combination of sodium chloride and potassium chloride.

The present compositions preferably include an effective amount of a chelating component. Any suitable, preferably ophthalmically acceptable, chelating component may be included in the present compositions, although ethylenediaminetetraacetic acid (EDTA), salts thereof and mixtures thereof are particularly effective. More preferably, the present compositions include chelating components in effective amounts less than about 0.05% (w/v) and still more preferably 0.02% (w/v) or less. Such reduced amounts of chelating component in the present compositions remain effective in providing the desired chelating and/or sequestering functions while, at the same time, are better tolerated in the eye, thereby reducing the risk of user discomfort and/or ocular irritation.

Any suitable, preferably ophthalmically acceptable buffer component may be included in the present composition. Phosphate, organic amine (e.g., tromethamine) or boric acid buffers are preferred, in an amount effective in maintaining the pH of the composition within a physiologically acceptable range.

Various combinations of two or more of the above noted components may be used in providing at least one of the benefits described herein. Therefore, each and every such combination is included within the scope of the present invention.

In one embodiment, the present compositions comprise: a liquid aqueous medium, CPC, in an amount effective to, in association with the remainder of the solution, disinfect a contact lens contacted with the composition; a non-ionic surfactant component in an amount effective in

cleaning a contact lens contacted with the composition; a phosphate buffer component in an amount effective in maintaining the pH of the composition within a physiologically acceptable range; an effective amount of a viscosity inducing component; and an effective amount of a tonicity component. The present compositions may also include an effective amount of a chelating or sequestering component, more preferably in a range of less than 0.05% (w/v). Each of the components, in the concentration employed, included in the solutions and the formulated solutions of the present invention generally are ophthalmically acceptable. In addition, each of the components (in the case of the CPC, in combination with the non-ionic surfactant as described above), in the concentration employed included in the present solutions usually is soluble in the liquid aqueous medium. The solution may also optionally include an additional antimicrobial component in an amount effective to, in association with the remainder of the solution, disinfect a contact lens contacted with the composition.

A solution or component thereof is "ophthalmically acceptable" when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissue. Preferably, each component of the present compositions is also compatible with the other components of the present compositions. The present compositions are more preferably substantially ophthalmically optimized. An ophthalmically optimized composition is one which, within the constraints of component chemistry, minimizes ocular response, or conversely delivers ophthalmic benefit to the lens wearing eye.

The presently useful additional antimicrobial components include chemicals which derive their antimicrobial activity through a chemical or physiochemical interaction with microbes or microorganisms, such as those contaminating a contact lens. Suitable additional antimicrobial components are those generally employed in ophthalmic applications and include, but are not

limited to, quaternary ammonium salts used in ophthalmic applications such as poly [dimethylimino-2-butene-1, 4-diyl] chloride, alpha - [4-tris (2-hydroxyethyl) ammonium] - dichloride (chemical registry number 75345-27-6, available under, the trademark Polyquaternium 1® from Onyx Corporation), benzalkonium halides, and biguanides, such as salts of alexidine, alexidine-free base, salts of chlorhexidine, hexamethylene biguanides and their polymers, and salts thereof, antimicrobial polypeptides, chlorine dioxide precursors, and the like and mixtures thereof. Generally, the hexamethylene biguanide polymers (PHMB), also referred to as polyaminopropyl biguanide (PAPB), have molecular weights of up to about 100,000. Such compounds are known and are disclosed in Ogunbiyi et al, U.S. Patent No. 4,759,595, the disclosure of which is hereby incorporated in its entirety by reference herein.

Generally, the antimicrobial component is present in the liquid aqueous medium at an ophthalmically acceptable or safe concentration such that the user can remove the disinfected lens from the liquid aqueous medium and thereafter directly place the lens in the eye for safe and comfortable wear. Alternatively, the antimicrobial component is present in the liquid aqueous medium at an ophthalmically acceptable or safe concentration and sufficient for maintaining preservative effectiveness. The additional antimicrobial components useful in the present invention preferably are present in the liquid aqueous medium in concentrations in the range of about 0.00001% to about 0.01% (w/v), and more preferably in concentrations in the range of about 0.00005 % to about 0.001% (w/v) and most preferably in concentrations in the range of about 0.00005 % to about 0.0005% (w/v).

The additional antimicrobial components suitable for inclusion in the present invention include chlorine dioxide precursors. Specific examples of chlorine dioxide precursors include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal

chlorites, and the like and mixtures thereof. Technical grade sodium chlorite is a very useful chlorine dioxide precursor. Chlorine dioxide containing complexes such as complexes of chlorine dioxide with carbonate, chlorine dioxide with bicarbonate and mixtures thereof are also included as chlorine dioxide precursors. The exact chemical composition of many chlorine dioxide precursors, for example, SCD and the chlorine dioxide complexes, is not completely understood. The manufacture or production of certain chlorine dioxide precursors is described in McNicholas, U.S. Patent 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor® by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc.

If a chlorine dioxide precursor is included in the present compositions, it generally is present in an effective preservative or contact lens disinfecting amount. Such effective preservative or disinfecting concentrations usually are in the range of about 0.002 to about 0.06% (w/v) of the present compositions. The chlorine dioxide precursors may be used in combination with other antimicrobial components, such as biguanides, biguanide polymers, salts thereof and mixtures thereof.

In the event that chlorine dioxide precursors are employed as antimicrobial components, the compositions usually have an osmolality of at least about 200 mOsmol/kg and are buffered to maintain the pH within an acceptable physiological range, for example, a range of about 6 to about 10.

In one embodiment, the additional antimicrobial component is non-oxidative. It has been found that reduced amounts of non-oxidative antimicrobial components, for example, in a range

of about 0.1 ppm to about 3 ppm or less than 5 ppm (w/v), in the present compositions are effective in disinfecting contact lenses and reduce the risk of such antimicrobial components causing ocular discomfort and/or irritation. Such reduced concentration of antimicrobial component is very useful when the antimicrobial component employed is selected from biguanides, biguanide polymers, salts thereof and mixtures thereof.

When a contact lens is desired to be disinfected by the present compositions, a total amount of antimicrobial component(s) effective to disinfect the lens is used. Generally, such an effective amount of the antimicrobial component reduces the microbial burden or load on the contact lens by one log order in three hours. More preferably, an effective amount of the disinfectant reduces the microbial load by one log order in one hour.

The buffer component is present in an amount effective to maintain the pH of the composition or solution in the desired range, for example, in a physiologically acceptable range of about 6 to about 7.5 or about 8.5. In particular, the solution has a pH in the range of about 7 to about 8. The buffer component preferably includes one or more phosphate or tromethamine (TRIS, 2-amino-2-hydroxymethyl-1,3-propanediol) or boric buffers, for example, combinations of monobasic phosphates, dibasic phosphates and the like, or tromethamine and tromethamine hydrochloride. Particularly useful phosphate buffers are those selected from phosphate salts of alkali and/or alkaline earth metals. Examples of suitable phosphate buffers include one or more of sodium phosphate dibasic ( $\text{Na}_2\text{HPO}_4$ ) sodium phosphate monobasic ( $\text{NaH}_2\text{PO}_4$ ) and potassium phosphate monobasic ( $\text{KH}_2\text{PO}_4$ ). The buffer may be a boric acid/sodium hydroxide buffer or a boric acid/sodium borate buffer. The buffer component may also include an amino acid such as taurine. The present buffer components frequently are used in amounts in a range of about 0.01% or about 0.02% to about 0.5% or about 1% (w/v).



The present compositions usually further comprise effective amounts of one or more additional components, such as a detergent or surfactant component; a viscosity inducing or thickening component; a chelating or sequestering component; a tonicity component; and the like and mixtures thereof. The additional component or components may be selected from materials which are known to be useful in contact lens care compositions and are included in amounts effective to provide the desired effect or benefit. When an additional component is included, it is generally compatible under typical use and storage conditions with the other components of the composition. For instance, the aforesaid additional component or components are substantially stable in the presence of the antimicrobial and buffer components described herein.

The non-ionic surfactant component generally is present in an amount effective in cleaning, that is to at least facilitate removing, and preferably effective to remove, debris or deposit material from, a contact lens contacted with the surfactant containing solution. Exemplary surfactant components include, but are not limited to, Tetronic 1307, Tetronic 1107, Tetronic 1304, Tetronic 904, Pluronic F87, and mixtures thereof.

The amount of non-ionic surfactant component present, if any, varies over a wide range depending on a number of factors, for example, the concentration of the CPC being used, the specific surfactant or surfactants being used, the other components in the composition and the like. Often the amount of surfactant is in the range of about 0.0003% or about 0.002% to about 0.1% or about 0.5% or about 1.0% (w/v).

The viscosity inducing components employed in the present solutions preferably are effective at low or reduced concentrations, compatible with the other components of the present solutions, and anionic and non-ionic. Such viscosity inducing components are effective to

enhance and/or prolong the cleaning and wetting activity of the surfactant component and/or condition the lens surface rendering it more hydrophilic (less lipophilic) and/or to act as a demulcent on the eye. Increasing the solution viscosity provides a film on the lens which may facilitate comfortable wearing of the treated contact lens. The viscosity inducing component may also act to cushion the impact on the eye surface during insertion and serves also to alleviate eye irritation.

Suitable viscosity inducing components include, but are not limited to, water soluble natural gums, cellulose-derived polymers and the like. Useful natural gums include guar gum, gum tragacanth and the like. Useful cellulose-derived viscosity inducing components include cellulose-derived polymers, such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, methyl cellulose, hydroxyethyl cellulose and the like. More preferably, the viscosity inducing agent is selected from cellulose derivatives (polymers) and mixtures thereof. A very useful viscosity inducing component is hydroxypropylmethyl cellulose (HPMC).

The viscosity inducing component is used in an amount effective to increase the viscosity of the solution, preferably to a viscosity in the range of about 1.5 to about 30, or even as high as about 750, cps at 25°C, preferably as determined by USP test method No. 911 (USP 23, 1995). To achieve this range of viscosity increase, an amount of viscosity inducing component of about 0.01% to about 5% (w/v) preferably is employed, with amounts of about 0.05% to about 0.5% being more preferred.

A chelating or sequestering component preferably is included in an amount effective to enhance the effectiveness of the antimicrobial component and/or to complex with metal ions to provide more effective cleaning of the contact lens.

A wide range of organic acids, amines or compounds which include an acid group and an amine function are capable of acting as chelating components in the present compositions. For example, nitrilotriacetic acid, diethylenetriaminepentacetic acid, hydroxyethylethylenediaminetriacetic acid, 1,2-diaminocyclohexane tetraacetic acid, hydroxyethylaminodiacetic acid, ethylenediamine-tetraacetic acid and its salts, polyphosphates, citric acid and its salts, tartaric acid and its salts, and the like and mixtures thereof, are useful as chelating components. Ethylenediaminetetraacetic acid (EDTA) and its alkali metal salts, are preferred, with disodium salt of EDTA, also known as disodium edetate, being particularly preferred.

The chelating component preferably is present in an effective amount, for example, in a range of about 0.01% and about 1% (w/v) of the solution.

In a very useful embodiment, particularly when the chelating component is EDTA, salts thereof and mixtures thereof, a reduced amount is employed, for example, in the range of less than about 0.05% (w/v) or even about 0.02% (w/v) or less. Such reduced amounts of chelating component have been found to be effective in the present compositions while, at the same time, providing for reduced cytotoxicity, discomfort and/or ocular irritation.

The liquid aqueous medium used is selected to have no substantial deleterious effect on the lens being treated, or on the wearer of the treated lens. The liquid medium is constituted to permit, and even facilitate, the lens treatment or treatments by the present compositions. The liquid aqueous medium advantageously has an osmolality in the range of at least about 200-mOsmol/kg to about 300 or about 350 mOsmol/kg. The liquid aqueous medium more preferably is substantially isotonic or hypotonic (for example, slightly hypotonic) and/or is ophthalmically acceptable.

The liquid aqueous medium preferably includes an effective amount of a tonicity component to provide the liquid medium with the desired tonicity. Such tonicity components may be present in the liquid aqueous medium and/or may be introduced into the liquid aqueous medium. Among the suitable tonicity adjusting components that may be employed are those conventionally used in contact lens care products, such as various inorganic salts. Sodium chloride and/or potassium chloride and the like are very useful tonicity components. The amount of tonicity component included is effective to provide the desired degree of tonicity to the solution. Such amount may, for example, be in the range of about 0.1% to about 1.5% (w/v). If a combination of sodium chloride and potassium chloride is employed, it is preferred that the weight ratio of sodium chloride to potassium chloride be in the range of about 2.5 to about 6 or about 8.

The amount of taurine useful in the present invention may be determined by objective clinical measures such as tear LDH release from corneal epithelial cells or fluorescein barrier permeability measurements or another means to evaluate ocular cell membrane integrity such as fluorescein or rose bengal staining. Yet another means to evaluate ocular cell membrane integrity is the use of confocal microscopy to measure epithelial cell area. In lieu of using tear LDH as a response factor, another inflammatory mediator may be measured in tears to indicate a beneficial effect from taurine. Useful amounts of taurine can also be determined by subjective clinical measures such as itching, lacrimation (tearing) and comfort. The amount of taurine useful in the present invention is generally from about 0.01 to about 2.0 w/v%. The preferred amount is 0.05 to 1.00 w/v%.

Methods for treating a contact lens using the herein described compositions are included within the scope of the invention. Such methods comprise contacting a contact lens with such a composition at conditions effective to provide the desired treatment to the contact lens.

The contacting temperature is preferred to be in the range of about 0°C to about 100°C, and more preferably in the range of about 10°C to about 60°C and still more preferably in the range of about 15°C to about 30°C. Contacting at or about ambient temperature is very convenient and useful. The contacting preferably occurs at or about atmospheric pressure. The contacting preferably occurs for a time in the range of about 5 minutes or about 1 hour to about 12 hours or more.

The contact lens can be contacted with the liquid aqueous medium by immersing the lens in the medium. During at least a portion of the contacting, the liquid medium containing the contact lens optionally may be agitated, for example, by shaking the container containing the liquid aqueous medium and contact lens, to at least facilitate removal of deposit material from the lens. After such contacting step, the contact lens optionally may be manually rubbed to remove further deposit material from the lens. The cleaning method optionally may also include rinsing the lens substantially free of the liquid aqueous medium prior to returning the lens to a wearer's eye.

The following examples, while not limiting, are illustrative of the invention.

The following is the procedure by which various antimicrobial agents and solutions are tested for their ability to reduce microbial loads over short periods of time, typically 24 hours and less. The procedure is a basic microbiology challenge test, which involves the inoculation of test product aliquots with a known number of viable cells of several test organisms, and assay for

the survivors at various time intervals. The results are used to calculate log drops at soak times and construct kill-curves (graphs of survivors versus time) if desired.

Candida albicans, ATCC 10231, is one of five organisms specified per FDA and ISO/CLI tests for the testing of contact lens disinfectants (FDA Premarket Notification (510k) Guidance Document for Contact Lens Care Products, Appendix A and B, May 1, 1997 and ISO/FDIS 14729: Ophthalmic optics-Contact lens care products- Microbiological requirements and test methods for products and regimens for hygienic management of contact lenses, January 2001). Contact lens disinfectants are also known as contact lens multi-purpose solutions when they are used for rinsing, cleaning, disinfection, storage and rewetting contact lenses. The five FDA/ISO specified test organisms are listed below:

Serratia marcescens, ATCC 13880

Staphylococcus aureus, ATCC 6538

Pseudomonas aeruginosa, ATCC 9027

Candida albicans, ATCC 10231

Fusarium solani, ATCC 36031

Candida albicans is often the most resistant of the five organisms to commonly used cationic antimicrobial agents in contact lens multi-purpose solutions. Thus, achievement of adequate antimicrobial activity against Candida is often the most difficult task to pass a particular disinfection efficacy standard. FDA and ISO guidelines specify two disinfection efficacy standards, indicated in the table below:

Stand Alone Disinfectant (Primary) Criteria:

| Organism             | Average log reduction at labeled soak time |
|----------------------|--|
| <u>S. marcescens</u> | 3.0 logs                                   |

|                      |          |
|----------------------|----------|
| <u>S. aureus</u>     | 3.0 logs |
| <u>P. aeruginosa</u> | 3.0 logs |
| <u>C. albicans</u>   | 1.0 log  |
| <u>F. solani</u>     | 1.0 log  |

Regimen-Dependent Disinfectant (Secondary) Criteria:

| Organism             | Average log reduction at labeled soak time |
|----------------------|--|
| <u>S. marcescens</u> | Minimum of 1.0 log per bacterium,          |
| <u>S. aureus</u>     | sum of all three bacteria log-drops        |
| <u>P. aeruginosa</u> | must be greater than or equal to 5.0 log   |
| <u>C. albicans</u>   | Stasis                                     |
| <u>F. solani</u>     | Stasis                                     |

The specific test procedure for testing antimicrobial activity against the five FDA/ISO specified test organisms is as follows (C. albicans is provided as a specific example): Test samples are sterile-filtered through a 0.22 micron sterile filter into sterile plastic high density polyethylene bottles or plastic flasks. A 10-mL aliquot of test sample is aseptically transferred into a sterile polystyrene plastic test tube. Sterile saline (0.90 w/v% NaCl) with 0.05 w/v% Polysorbate 80 (SS + TWEEN) (Tween 80 (Uniquema, Wilmington, Delaware)) is transferred into a separate control tube. All samples and control are stored at 20-25 °C throughout the duration of the test.

Test cultures of Candida albicans, ATCC 10231 are prepared in the conventional manner. Candida albicans cultures are grown on agar slants from primary frozen, lyophilized or “Culti-loop®” cultures. Three mL of sterile 0.9% saline is used to gently dislodge culture growth from the agar surface. The resulting harvest is transferred to an appropriate screw cap test tube containing glass beads and vortexed for approximately one minute. The vortexed harvest is diluted as needed with sterile 0.9% saline to prepare the culture inoculum with a concentration of

1 x 10<sup>8</sup> CFU/mL. Fifty microliters of culture inoculum is added to 10.0 mL of each test sample and control, so that the final inoculum level is in the range of 1 x 10<sup>5</sup> to 1 x 10<sup>6</sup> CFU(colony forming units) per mL of Candida albicans, ATCC 10231. Each sample and control tube is vortexed briefly to disperse the inoculum. Contact time intervals for testing activity against Candida are typically 4 or 6 hours, to conform to the intended product label instructions for contact lens soak time.

Aerobic Plate Count Methods are performed in order to quantitate test samples for their levels of survivors. At appropriate assay times, 0.5 mL well-vortexed aliquots are removed from sample tubes and added to glass test tubes containing 4.5 mL Letheen Neutralizing Broth media (Berton, Dickinson and Company, Sparks, Maryland). After a previously determined, validated neutralizing time period, these samples are diluted 10-fold through serial dilutions using glass test tubes containing 4.5 mL Letheen Neutralizing Broth media. Aliquots of 0.1 mL are removed from each dilution tube and spread-plate applied to agar plates containing Sabouraud Dextrose Agar (SAB)(Berton, Dickinson and Company, Sparks, Maryland). 10<sup>1</sup> to 10<sup>4</sup> CFU/mL survivor levels are quantitated. The SS + TWEEN control samples are quantitated only at time = 0 using 3 serial 10-fold dilutions, in order to determine the actual levels of challenge organisms initially present per mL of sample (initial inoculum). Recovery agar plates are incubated at 20-25°C for 3-5 days.

Numbers of colony-forming-units (CFU) are counted for each countable agar plate (generally between 8-80 colonies per plate for Candida plates). Log-drops in CFU/mL are determined for each sample at each time interval by converting the total number of survivors at each time interval to a base-10 logarithm and subtracting this from the base-10 logarithm



equivalent of the initial inoculum of the SS + TWEEN control. Log reduction values can be plotted against contact time (the particular test time interval) or evaluated as is.

As noted above in the Background of the Invention section, non-ionic surfactants are commonly used in microbiology tests to stop a quaternary ammonium/alkylamine activity. One of the significant differences between a contact lens care system and re-circulating water systems is that the former requires the presence of a large amount of a surfactant as a cleaning agent while the latter is not compatible with surfactants due to foaming problems. Typically, non-ionic surfactants and polymeric/non-polymeric quaternary ammoniums form ion-pair or precipitate in an aqueous solution and therefore, cannot be mixed together. The presence of non-ionic surfactants at a cleaning agent level usually would cause a significant, if not complete, loss of antimicrobial activity for non-polymeric quaternary ammonium or alkylamine. As shown in Table 1, the addition of the non-ionic surfactant tocopherol polyethylene glycol succinate ("TPGS") halts the ammonium/alkylamine activity.

Table 1.

| Formulation              | % w/v    | % w/v    | % w/v    |
|--------------------------|----------|----------|----------|
| Cetylpyridinium Chloride | 9.5 ppm  | 9.5 ppm  | 9.5 ppm  |
| TPGS                     | 76 ppm   | 143 ppm  | 238 ppm  |
| Taurine                  | 0.05     | 0.05     | 0.05     |
| Propylene Glycol         | 0.50     | 0.50     | 0.50     |
| Tetronic®1307            | 0.05     | 0.05     | 0.05     |
| EDTA, Disodium           | 0.01     | 0.01     | 0.1      |
| HPMC                     | 0.15     | 0.15     | 0.15     |
| Tromethamine             | 0.021    | 0.021    | 0.021    |
| Tromethamine.HCl         | 0.055    | 0.055    | 0.55     |
| NaCl                     | 0.65     | 0.65     | 0.65     |
| KCl                      | 0.14     | 0.14     | 0.14     |
| pH 7.8                   |          |          |          |
|                          | Log Drop | Log Drop | Log Drop |

|                      |      |      |      |
|----------------------|------|------|------|
| <i>S. marcescens</i> | 2.18 | 0.58 | 0.52 |
| <i>S. aureus</i>     | 4.8  | 3.1  | 0.63 |
| <i>P. aeruginosa</i> | 4.86 | 4.86 | 3.61 |
| <i>C. albicans</i>   | 2.92 | 0.97 | 0.12 |
| <i>F. solani</i>     | 3.36 | 1.69 | 1.06 |

As may be seen from the log drop in activity, caused by the increase in TPGS, a non-ionic surfactant, one must carefully design the solution of the present invention so that the surfactant does not decrease the increase in antimicrobial activity brought about by CPC.

A similar reduction in antimicrobial activity may be seen when the Tween 80 concentration increases to a level of 176 ppm. Such level is typically required in a cleaning and disinfecting solution.

TABLE 2.

| Ingredient                                    | % w/w    | % w/w    |
|---|----------|----------|
| CPC   | 5 ppm    | 5 ppm    |
| Tween 80                                      | 176 ppm  | 20 ppm   |
| Polyquat-1                                    | 0.77 ppm | 0.77 ppm |
| HPMC  | 0.15     | 0.15     |
| Tetronic® 1307                                | 0.05     | 0.05     |
| Edate Disodium                                | 0.01     | 0.01     |
| Propylene Glycol                              | 0.50     | 0.50     |
| NaCl  | 0.55     | 0.55     |
| KCl   | 0.14     | 0.14     |
| Sodium phosphate, monobasic, H <sub>2</sub> O | 0.01     | 0.01     |
| Sodium phosphate, dibasic, 7H <sub>2</sub> O  | 0.12     | 0.12     |
| pH 7.3  |          |          |
|   | Log Drop | Log Drop |
| <i>S. marcescens</i>                          | 2.77     | >4.85    |
| <i>S. aureus</i>                              | 1.88     | >4.74    |
| <i>P. aeruginosa</i>                          | >4.63    | >4.63    |
| <i>C. albicans</i>                            | 0.1      | 4.46     |

|                  |      |      |
|------------------|------|------|
| <b>F. solani</b> | 0.52 | 4.15 |
|------------------|------|------|

It is easily seen from the data in Table 2 that CPC, in association with a predetermined concentration of a non-ionic, poly(oxypropylene)-poly(oxyethylene) block copolymer surfactant has strong antimicrobial activity. In fact, as shown in Table 3, the effect of a non-ionic surfactant on CPC's antimicrobial activity may be seen even when the surfactant concentration is far below its critical micelle formation concentration (cmc) (cmc = 200 ppm for TPGS in water).

TABLE 3

| <b>Ingredient</b>                             | <b>% w/w</b>    | <b>% w/w</b>    |
|---|-----------------|-----------------|
| CPC   | 5 ppm           | 5 ppm           |
| TPGS  | 40 ppm          | 20 ppm          |
| Polyquaternium-1                              | 0.75 ppm        | 0.75 ppm        |
| Taurine                                       | 0.05            | 0.05            |
| Propylene Glycol                              | 0.50            | 0.50            |
| Tetronic 1307                                 | 0.05            | 0.05            |
| EDTA, Disodium                                | 0.01            | 0.01            |
| HPMC  | 0.15            | 0.15            |
| Sodium phosphate, dibasic, 7H <sub>2</sub> O  | 0.12            | 0.12            |
| Sodium phosphate, monobasic, H <sub>2</sub> O | 0.01            | 0.01            |
| NaCl  | 0.55            | 0.55            |
| KCl   | 0.14            | 0.14            |
| pH 7.3  |                 |                 |
|   | <b>Log drop</b> | <b>Log drop</b> |
| <i>S.marcesens</i>                            | >5.07           | >5.07           |
| <i>S.aureus</i>                               | 4.72            | 3.74            |
| <i>P. aeruginosa</i>                          | >4.86           | >4.86           |
| <i>C.albicans</i>                             | 1.36            | 2.54            |
| <i>F.solani</i>                               | 2.64            | 3.35            |

As shown by the formulations and resulting log reductions shown in Tables 4 and 5, the antimicrobial activity of CPC is enhanced if selected non-ionic surfactants, for example poly(oxypropylene)-poly(oxyethylene) block copolymer, non-ionic surfactants (e.g., Tetronic or Pluronic non-ionic surfactants), are used. The data shown in Tables 4 and 5 illustrates that CPC at low concentrations has effective antimicrobial activity with either Pluronic F87 or Tetronic 1307 at a concentration range that is typically used in cleaning solutions.

TABLE 4.

| Formulation          | w/v %    | w/v %    |
|----------------------|----------|----------|
| CPC                  | 2.0 ppm  | 2.0 ppm  |
| Pluronic F87         | 0.05     | 0.2      |
| Taurine              | 0.05     | 0.05     |
| NaCl                 | 0.53     | 0.53     |
| KCl                  | 0.14     | 0.14     |
| Boric acid           | 0.48     | 0.48     |
| Sodium borate        | 0.16     | 0.16     |
| Edatate Disodium     | 0.05     | 0.05     |
| pH 7.8               |          |          |
|                      | Log Drop | Log Drop |
| <u>S.marcescens</u>  | 4.73     | 3.56     |
| <u>S.aureus</u>      | >4.89    | 3.16     |
| <u>P. aeruginosa</u> | 4.89     | 3.89     |
| <u>C.albicans</u>    | >4.40    | 2.61     |
| <u>F. solani</u>     | 4.23     | 3.05     |

TABLE 5

| Formulation | #1    | #2    | #5    |
|-------------|-------|-------|-------|
|             | % w/v | % w/v | % w/v |

| CPC   | 7 ppm    | 5 ppm    | 3 ppm    |
|---|----------|----------|----------|
| Taurine                                       | 0.05     | 0.05     | 0.05     |
| Propylene glycol                              | 0.5      | 0.5      | 0.5      |
| Tetronic 1307                                 | 0.05     | 0.05     | 0.05     |
| EDTA, Disodium                                | 0.01     | 0.01     | 0.01     |
| HPMC  | 0.15     | 0.15     | 0.15     |
| Sodium phosphate, dibasic, 7H <sub>2</sub> O  | 0.12     | 0.12     | 0.12     |
| Sodium phosphate, monobasic, H <sub>2</sub> O | 0.01     | 0.01     | 0.01     |
| NaCl  | 0.55     | 0.55     | 0.55     |
| KCl   | 0.14     | 0.14     | 0.14     |
| pH 7.3  |          |          |          |
|   | Log Drop | Log Drop | Log Drop |
| <u><b>S.marcescens</b></u>                    | >4.81    | >4.81    | 3.91     |
| <u><b>S.aureus</b></u>                        | >4.00    | >4.00    | >4.00    |
| <u><b>P. aeruginosa</b></u>                   | >4.79    | 3.79     | 4.79     |
| <u><b>C.albicans</b></u>                      | >4.46    | >4.46    | 3.76     |
| <u><b>F. solani</b></u>                       | >4.23    | >4.23    | 2.45     |

By way of comparison, Table 6 shows that the effect of a conventional non-ionic surfactant on the activity of a polyquaternary ammonium antimicrobial agent is negligible, even at fifty times more than what is needed for cleaning. The polyquaternary ammonium antimicrobial used in this test is Polyquaternium-1. Based on this data the inventors conclude that, in order to use CPC as an antimicrobial agent for contact lens disinfection at a low concentration level, the use of typical non-ionic surfactants consisting of an alkyl hydrophobic part on one side and a hydrophilic part on the other side (e.g., TPGS) is not beneficial to CPC's activity. Preferably, the ratio of such non-ionic surfactants consisting of an alkyl hydrophobic part on one side and a hydrophilic part on the other side to CPC should be kept as low as possible or such surfactants even be avoided or removed.

TABLE 6

| Formulation       | % w/v           | % w/v      |
|-------------------|-----------------|------------|
| Polyquaternium-1  | 3 ppm           | 3 ppm      |
| TPGS              | 0.00            | 10,000 ppm |
| Boric acid        | 0.6             | 0.6        |
| HPMC              | 0.15            | 0.15       |
| Sodium Borate     | 0.035           | 0.035      |
| NaCl              | 0.4             | 0.4        |
| KCl               | 0.14            | 0.14       |
| pH 7.8            |                 |            |
|                   | <b>Log Drop</b> |            |
| <b>S.aureus</b>   | 2.85            | 2.34       |
| <b>C.albicans</b> | 3.45            | 3.6        |

Table 7 shows the effect that various types of buffers have on CPC antimicrobial activity.

As may be seen, the antimicrobial efficacy is higher with boric buffers than that which is shown using a phosphate buffer for 4 of the 5 test organisms. By contrast, the anti-bacteria activities are the same for the boric and Tris buffer solutions. One can also see that the anti-fungal activities of Tris buffer are at the same level as those of phosphate buffer solution, and both buffer solutions have lower anti-fungal activities than the boric buffer solutions.

TABLE 7

| Formulation | #1    | #2    | #3    | #4    |
|-------------|-------|-------|-------|-------|
|             | % w/v | % w/v | % w/v | % w/v |
| CPC         | 2 ppm | 2 ppm | 2 ppm | 2 ppm |
| Taurine     | 0.05  | 0.05  | 0.05  | 0.05  |
| NaCl        | 0.55  | 0.55  | 0.59  | 0.59  |
| KCl         | 0.14  | 0.14  | 0.14  | 0.14  |
| HPMC        | 0.15  | 0.15  | 0.15  | 0.15  |

|   |      |      |      |       |
|---|------|------|------|-------|
| EDTA, Disodium                                | 0.01 | 0.01 | 0.01 | 0.01  |
| Tetronic®1307                                 | 0.05 | 0.05 |      |       |
| Pluronic® F87                                 |      |      | 0.05 | 0.05  |
| Propylene Glycol                              | 0.5  |      |      | 0.5   |
| Sodium phosphate, dibasic, 7H <sub>2</sub> O  | 0.12 |      |      |       |
| Sodium phosphate, monobasic, H <sub>2</sub> O | 0.01 |      |      |       |
| Boric Acid                                    |      | 0.48 | 0.48 |       |
| Sodium Borate                                 |      | 0.16 | 0.16 |       |
| Tromethamine                                  |      |      |      | 0.021 |
| Tromethamine.HCl                              |      |      |      | 0.055 |
| pH  | 7.3  | 7.8  | 7.8  | 7.8   |
| Log-drop at 6 hours                           |      |      |      |       |
| <i>S. marcescens</i>                          | 2.3  | 4.9  | 4.1  | 4.6   |
| <i>S. aureus</i>                              | 4.0  | 4.0  | 4.4  | 4.2   |
| <i>P. aeruginosa</i>                          | 2.3  | 4.8  | 4.3  | 4.0   |
| <i>C. albicans</i>                            | 2.1  | 3.4  | 2.8  | 2.2   |
| <i>F. solani</i>                              | 1.8  | 4.2  | 3.8  | 1.9   |

By way of further example, Table 8 demonstrates that CPC in boric acid/sodium hydroxide buffer is very efficacious. At 1 ppm CPC level, the solution can meet the disinfecting criteria for a stand-alone product.

TABLE 8

| Formulation    | % w/v | % w/v   | % w/v | % w/v   |
|----------------|-------|---------|-------|---------|
| CPC            | 1 ppm | 1.5 ppm | 2 ppm | 2.5 ppm |
| Boric acid     | 0.6   | 0.6     | 0.6   | 0.6     |
| NaOH (1N)      | 6.75  | 6.75    | 6.75  | 6.75    |
| HPMC           | 0.15  | 0.15    | 0.15  | 0.15    |
| EDTA, Disodium | 0.01  | 0.01    | 0.01  | 0.01    |
| Taurine        | 0.05  | 0.05    | 0.05  | 0.05    |
| NaCl           | 0.59  | 0.59    | 0.59  | 0.59    |
| KCl            | 0.14  | 0.14    | 0.14  | 0.14    |
| Pluronic® F87  | 0.05  | 0.05    | 0.05  | 0.05    |

|                                  |          |          |          |          |
|----------------------------------|----------|----------|----------|----------|
| PEG 400                          | 0.1      | 0.1      | 0.1      | 0.1      |
| pH 7.7                           |          |          |          |          |
|                                  | Log Drop | Log Drop | Log Drop | Log Drop |
| <b><i>S.marcescens</i> 13880</b> | 3.32     | 3.35     | 4.1      | 4.5      |
| <b><i>S. aureus</i> 6538</b>     | 3.63     | 3.89     | >4.67    | >4.67    |
| <b><i>P.aeruginosa</i> 9027</b>  | >4.65    | >4.65    | >4.65    | >4.65    |
| <b><i>C.albicans</i> 10231</b>   | 2.22     | 2.55     | 3        | 4.45     |
| <b><i>F.solani</i> 36031</b>     | 1.64     | 2.11     | 1.8      | 2.56     |

The inventors have further determined that the antimicrobial activity of a CPC solution according to the present invention may be further enhanced if one or more additional antimicrobial agents are added. By way of example, Table 9 shows that, when polyquaternium-1 is added to a CPC disinfecting solution, antimicrobial activity is significantly increased.

TABLE 9

| Formulation                                   | % w/w              | % w/w    |
|---|--------------------|----------|
| CPC   | 5 ppm              | 5 ppm    |
| Polyquaternium-1                              | 0                  | 0.75 ppm |
| Tween 80                                      | 20 ppm             | 20 ppm   |
| Taurine                                       | 0.05               | 0.05     |
| Propylene Glycol                              | 0.5                | 0.5      |
| Tetronic® 1307                                | 0.05               | 0.05     |
| EDTA, Disodium                                | 0.01               | 0.01     |
| HPMC  | 0.15               | 0.15     |
| Sodium phosphate, dibasic, 7H <sub>2</sub> O  | 0.12               | 0.12     |
| Sodium phosphate, monobasic, H <sub>2</sub> O | 0.01               | 0.01     |
| NaCl  | 0.55               | 0.55     |
| KCl   | 0.14               | 0.14     |
| pH 7.3  |                    |          |
|   | Log drop at 6 hour |          |
| <b><i>S.marcescens</i> 36031</b>              | 3.3                | >5.07    |
| <b><i>S.aureus</i> 6538</b>                   | 4.54               | >5.02    |
| <b><i>P.aeruginosa</i> 9027</b>               | >4.86              | >4.86    |



|                          |      |      |
|--------------------------|------|------|
| <i>C. albicans</i> 10231 | 3.17 | 2.93 |
| <i>F. solani</i> 36031   | 3.48 | 3.26 |

Further by way of example, Table 10 shows that the inclusion of either polyquaternium-1 or PHMB to a CPC disinfecting solution increases antimicrobial activity.

TABLE 10.

| Formulation                                   | #3       | #6       | #9      |
|---|----------|----------|---------|
|   | % w/v    | % w/v    | % w/v   |
| CPC   | 2 ppm    | 2 ppm    | 2 ppm   |
| PHMB  | 0.00     | 0.1 ppm  | 0.00    |
| Polyquaternium-1                              | 0.00     | 0.00     | 0.4 ppm |
| Taurine                                       | 0.05     | 0.05     | 0.05    |
| Propylene Glycol                              | 0.5      | 0.5      | 0.5     |
| Tetronic® 1307                                | 0.05     | 0.05     | 0.05    |
| EDTA, Disodium                                | 0.01     | 0.01     | 0.01    |
| HPMC  | 0.15     | 0.15     | 0.15    |
| Sodium phosphate, dibasic, 7H <sub>2</sub> O  | 0.12     | 0.12     | 0.12    |
| Sodium phosphate, monobasic, H <sub>2</sub> O | 0.01     | 0.01     | 0.01    |
| NaCl  | 0.55     | 0.55     | 0.55    |
| KCl   | 0.14     | 0.14     | 0.14    |
| pH 7.3  |          |          |         |
|   | Log Drop | Log Drop |         |
| <i>S.marcesens</i>                            | 2.26     | 3.46     | 3.76    |
| <i>S.aureus</i>                               | 3.95     | 3.51     | 3.65    |
| <i>P. aeruginosa</i>                          | 2.26     | 4.74     | 4.74    |
| <i>C.albicans</i>                             | 2.1      | 1.96     | 2.87    |
| <i>F.solani</i>                               | 1.76     | 1.76     | 1.7     |

The inventors have additionally determined that, at the concentrations set forth herein, CPC has low build-up in contact lenses. In order to compare this build-up with buildup of other known antimicrobials, a comparison was performed between a solution according to the present

invention and OPTI-FREE® Express® (Alcon Laboratories, Fort Worth, Texas), a commercially available multi-purpose solution.

In addition to another antimicrobial agent, the OPTI-FREE® Express® solution contains 5 ppm myristamidopropyl dimethylamine (MAPD), which is a quaternary ammonium at physiological pH. The accumulation of MAPD in lenses from the OPTI-FREE® Express® solution is deemed non-irritating to the eye.

Table 11 shows that the antimicrobial activity of formulation #5 in shown in Table 5, above, which contains 3 ppm CPC, is similar to that of the OPTI-FREE® Express® solution. Tables 12 and 13 are the CPC and MAPD uptake and release data for 2 types of lenses with the CPC formulation shown in Table 5 above and the OPTI-FREE® Express® solution respectively. In each cycle, each lens was soaked in a lens case with 3.5 ml of the test solution for 15 hours to measure lens uptake and with 2 ml saline for 9 hours to measure lens release. For this test, two commonly-available lenses were used: the Acuvue® lens (Johnson & Johnson Corporation, New Brunswick, New Jersey) and the Purevision™ lens (Bausch & Lomb Incorporated, Rochester New York).

**TABLE 11.**

| Formulation          | CPC<br>Formulation #5 in<br>Example 5 | OPTI-FREE® Express®<br>Lot#: 50473F<br>Exp. 06/05 |
|----------------------|---------------------------------------|---|
|                      | Log Drop                              | Log Drop  |
| <i>S.marcesens</i>   | 3.91                                  | 3.37  |
| <i>S.aureus</i>      | 4.00                                  | 3.05  |
| <i>P. aeruginosa</i> | 4.79                                  | 4.86  |
| <i>C.albicans</i>    | 3.76                                  | 3.11  |
| <i>F.solani</i>      | 2.45                                  | 3.3   |

TABLE 12.

| Cycles | Acuvue® Lenses         |                           | Purevision® Lenses     |                           |
|--------|------------------------|---------------------------|------------------------|---------------------------|
|        | Release from lens (µg) | Accumulation in Lens (µg) | Release from lens (µg) | Accumulation in Lens (µg) |
| 1      | 1.0                    | 4.5                       | 1.0                    | 4.4                       |
| 2      | 0.8                    | 8.9                       | 0.7                    | 10.3                      |
| 3      | 1.0                    | 14.1                      | 0.5                    | 17.3                      |

TABLE 13.

| Cycles | Acuvue® Lenses         |                           | Purevision® Lenses     |                           |
|--------|------------------------|---------------------------|------------------------|---------------------------|
|        | Release from lens (µg) | Accumulation in Lens (µg) | Release from lens (µg) | Accumulation in Lens (µg) |
| 1      | 2.5                    | 7.9                       | 0.2                    | 18.3                      |
| 2      | 3.9                    | 10.1                      | 0.2                    | 33.9                      |
| 3      | 3.6                    | 12.4                      | 0.6                    | 48.1                      |

The results show that MAPD in the Opti-free® solution accumulates more in the lenses and releases more from the lenses than does CPC. It would be understood by one of ordinary skill in the art that the relative amounts released due to such saline soaking will approximate the relative amounts of antimicrobials released in a user's eye during the same wear time. As is well known, the higher amount of antimicrobial agent accumulation and release can be a cause of eye irritation. Since lower amounts of CPC than MAPD are released into the saline, and the accumulation of MAPD in lenses from the OPTI-FREE® Express® solution is deemed non-irritating to the eye, using low amounts of CPC can result in a non-irritating product to the eye.

The solutions according to the above examples may be used, for example, to clean contact lenses. In this embodiment of the invention, approximately three (3) ml of this solution is introduced into a lens vial containing a protein and lipid, oily deposit laden, hydrophilic or soft contact lens. The contact lens is maintained in this solution at room temperature for at least about four (4) hours. This treatment is effective to disinfect the contact lens. In addition, it is found that a substantial portion of the deposits previously present on the lens has been removed. This demonstrates that this solution has substantial passive contact lens cleaning ability. Passive cleaning refers to the cleaning which occurs during soaking of a contact lens, without mechanical or enzymatic enhancement.

After this time, the lens is removed from the solution and is placed in the lens wearer's eye for safe and comfortable wear. Alternately, after the lens is removed from the solution, it is rinsed with another quantity of this solution and the rinsed lens is then placed in the lens wearer's eye for safe and comfortable wear.

Alternatively, the solutions provided in the above-referenced examples may be used, for example, to wet or rewet contact lenses. A hydrophilic contact lens is ready for wear. In order to facilitate such wearing, one or two drops of one of the above solutions is placed on the lens immediately prior to placing the lens in the lens wearer's eye. The wearing of this lens is comfortable and safe.

Alternatively, a lens wearer wearing a contact lens may apply one or two drops of one of the above solutions in the eye wearing the lens. This effects a re-wetting of the lens and provides for comfortable and safe lens wear.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.